Human Biomarkers of Rapid Antidepressant Effects

Carlos A. Zarate Jr., Daniel C. Mathews, and Maura L. Furey

Mood disorders such as major depressive disorder and bipolar disorder—and their consequent effects on the individual and society—are among the most disabling and costly of all medical illnesses. Although a number of antidepressant treatments are available in clinical practice, many patients still undergo multiple and lengthy medication trials before experiencing relief of symptoms. Therefore a tremendous need exists to improve current treatment options and to facilitate more rapid, successful treatment in patients suffering from the deleterious neurobiological effects of ongoing depression. Toward that end, ongoing research is exploring the identification of biomarkers that might be involved in prevention, diagnosis, treatment response, severity, or prognosis of depression. Biomarkers evaluating treatment response will be the focus of this review, given the importance of providing relief to patients in a more expedient and systematic manner. A novel approach to developing such biomarkers of response would incorporate interventions with a rapid onset of action—such as sleep deprivation or intravenous drugs (e.g., ketamine or scopolamine). This alternative translational model for new treatments in psychiatry would facilitate shorter studies, improve feasibility, and increase higher compound throughput testing for these devastating disorders.

Key Words: Antidepressant, biomarker, cholinergic, depression, glutamate, ketamine, muscarinic, *N*-methyl-D-aspartate, scopolamine, sleep deprivation

Mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD)—and their consequent impairments on the individual, family, work force, and society—are among the most disabling and costly of all medical illnesses (1). The serendipitous discovery of the mood-enhancing effects of antituberculosis drugs in the 1950s introduced biological targets (i.e., serotonin and norepinephrine neurotransmitters) that were initially pursued to decipher the etiology and pathogenesis of MDD. Our increasing knowledge of these neurotransmitter systems led to the creation of a number of antidepressant drugs (e.g., tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors) currently being used in standard clinical practice. Nevertheless, many patients continue to undergo multiple and lengthy medication trials before experiencing relief of symptoms, and many do not respond to the current array of antidepressant agents. Furthermore, until full antidepressant effects manifest, patients experience considerable disruption to their lives and remain at risk for suicidal behavior. More importantly, individuals continue to be exposed to the deleterious neurobiological effects associated with ongoing depression. Thus, a tremendous need exists to facilitate more rapid and effective treatments for patients with mood disorders.

In developing any new therapeutic, the ability to assess both efficacy and safety is paramount. Testing these endpoints in clinical trials often requires significant time and has contributed to the escalating cost of validating investigational new drugs. In psychiatric and central nervous system (CNS) trials, developing biomarkers could provide surrogate indices of clinically relevant endpoints. Similarly, biomarkers could contribute to insights with regard to neurobiological correlates of treatment response (2). For this review, a biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" (3). Mood disorders research has focused on identifying biomarkers that might be involved in prevention, diagnosis, treatment response, severity, or prognosis—although their value in terms of personalizing treatment remains unclear (4). Table S1 in Supplement 1 broadly summarizes common biomarker tools used in treatment trials for mood disorders. Biomarkers evaluating rapid treatment response will be the focus of this review, given the significance of providing relief to patients in a more expedient and systematic manner.

One prominent limitation for developing biomarkers of response for existing traditional antidepressants is that many of these treatments require 6 weeks or more to exert an adequate treatment response. Other similar limitations are highlighted in Table S2 in Supplement 1. A novel approach that would resolve some of these limitations is the incorporation of interventions with a rapid onset of action (e.g., intravenous ketamine or scopolamine). This alternative translational approach could ultimately facilitate shorter studies, improve feasibility, and promote testing of putative biomarkers with overall higher compound throughput. Moreover, once such biomarkers are identified, they can be used a priori to guide additional research by classifying patients on the basis of expected clinical response to treatment.

Sleep Deprivation

Case observations of sleep deprivation (SD) in the early 1970s provided the first evidence that this treatment modality is a rapid-acting, nonpharmacological antidepressant therapy (5). Since then, several studies have demonstrated relatively rapid reversal (24–48 hours) of depressive symptoms in approximately 40%–60% of depressed patients (6). The SD interventions include total sleep deprivation (TSD) (studies vary from 26–36 to 36–40 hours) (5), partial sleep deprivation (approximately 20 hours, often with less-pronounced antidepressant effects) (7), and selective rapid eye movement (REM) SD.

Multiple biological factors have been implicated in the neurobiological mechanisms underlying the rapid antidepressant effects associated with SD, and a detailed review of these studies is beyond the scope of this article. However, Table 1 highlights much of the past work evaluating potential human biomarkers to

From the Experimental Therapeutics and Pathophysiology Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland.

Address correspondence to Carlos A. Zarate Jr., M.D., National Institute of Mental Health, National Institutes of Health, 10 Center Drive, CRC, 7 Southeast Unit, Room 7-3465, Bethesda, Maryland, 20892; E-mail: zaratec@mail.nih.gov.

Received Sep 17, 2012; revised Nov 13, 2012; accepted Nov 30, 2012.

Table 1. Biomarkers Used to Predict Treatment Response to SD

Biomarkers in SD	Design	Results	Reference
Neurophysiological			
EEG	$n = 16$ MDD, TSD	Responders to treatment were rated as significantly more depressed and revealed a more "depressed" EEG sleep pattern before sleep deprivation than NRs.	Duncan *et al.* (20)
	$n = 16$ MDD, TSD/SPA	SD responders showed a steady decrease of SWA across successive NREM episodes; a high DSR positively predicted SD response.	Nissen *et al.* (21)
	$n = 33$ MDD, PSD/TSD	With cutoffs of 30%, 35%, 40%, and 50% to dichotomize responders and NRs, PSG variables were evaluated for between-group differences; continuity differed between responders and NRs on baseline and recovery nights; no response cutoff tested was clearly "best" in terms of detecting the most PSG differences between groups.	Clark *et al.* (75)
	$n = 17$ MDD, BSL/SWD/RCV	Reduction in depressive symptoms correlated with the overnight dissipation of fronto-central SWA on baseline sleep, the rebound in right frontal all-night SWA on recovery sleep, and the amount of REM sleep on the SWD night.	Landsness *et al.* (22)
Auditory-evoked potentials	$n = 17$ depressed inpatients, TSD	The most prominent changes (responders and NRs) were found for the amplitude of the P300 component. Responders showed smaller N1 amplitudes before TSD but a higher increase after TSD than NRs.	Danos *et al.* (76)
Neuroimaging			
SPECT/HMPAO	$n = 10$ MDD - melancholic, TSD	All depressed patients ($n = 5$) showed relative hypoperfusion in the left anterolateral PFC before and after TSD; responders showed hyperperfusion in limbic system at baseline with reduction in limbic region after TSD.	Ebert *et al.* (77)
	$n = 20$ (15 MDD, 2 BD, 3 dysthymic), TSD	Responders ($n = 11$) showed increased CBF to left temporal and mainly right parietal regions; CBF values and the severity of depression correlated inversely.	Volk *et al.* (78)
	$n = 20$ MDD, melancholic, TSD	Before TSD, responders ($n = 11$) showed hyperperfusion in the right ACC and in the right and left fronto-orbital cortex and basal cingulate gyrus.	Ebert *et al.* (79)
	$n = 10$ MDD, TSD	Responders ($n = 5$) showed decrease of basal ganglia D2 receptor occupancy after TSD compared with NRs; data suggests enhanced dopamine release in responders.	Ebert *et al.* (80)
	$n = 15$ (13 MDD, 2 BD), PSD	Responders ($n = 9$) to PSD had higher perfusion in the right OFC than NRs before PSD; multiple regression analysis showed right orbitofrontal/basal cingulate perfusion before PSD, and left inferior temporal perfusion after PSD, as fairly accurate predictors of change in depression scores.	Volk *et al.* (81)
	$n = 14$ (12 MDD, 2 BD), TSD	Before TSD, responders ($n = 8$) had higher anterior cingulate perfusion than the NRs that normalized after TSD; baseline left hypoperfusion in left PFC in all patients, which responders normalized on remission.	Holthoff *et al.* (82)
PET/FDG	$n = 15$ MDD, TSD	Depressed responders ($n = 4$) had higher cingulate cortex metabolic rate than depressed NRs before TSD; this normalized after TSD.	Wu *et al.* (83)
	$n = 6$ MDD, elderly, TSD	Greatest reductions in normalized, relative glucose metabolism after TSD were observed in the ACC (Brodmann area 24); results persisted after recovery sleep and antidepressant treatment (paroxetine).	Smith *et al.* (84)
	$n = 36$ MDD, TSD	Responders ($n = 12$) had higher metabolic rates in the medial PFC, ventral ACC (Brodmann area 24), and posterior subcallosal gyrus at baseline than depressed NRs and control subjects; responders had decreases in the medial PFC and frontal pole after TSD.	Wu *et al.* (85)
	$n =$12 MDD, elderly, TSD	Early metabolic alterations in the right cingulate gyrus and the persistence of these adaptive changes were associated with improvement in depressive symptoms.	Smith *et al.* (86)
	$n = 6$ BD/MDD, TSD	Positive correlations (decreased depression with reduced relative cerebral glucose metabolism) were found in the inferior frontal gyrus and inferior frontal/orbital frontal cortex; negative correlations were found in the dorsolateral prefrontal cortex.	Wu *et al.* (16)